

# Epidemiology and therapy of symptomatic lymphoceles after robot-assisted radical prostatectomy (RARP)

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**Background:** Lymphoceles are a common postoperative complication after radical prostatectomy with pelvic lymphadenectomy. Therapeutic options include cannulation and drainage (CD), drainage and instillation (DI), or laparoscopic fenestration (LF). The aim of this study was to investigate the epidemiology of symptomatic lymphoceles (SLC) and evaluate the treatment options.

**Methods:** We retrospectively analysed all patients who underwent robot-assisted radical prostatectomy (RARP) at our clinic from January 1, 2014 to December 31, 2018. All documented lymphoceles of these patients were recorded and analysed with regard to symptoms, possible infection and the treatment option (or options) chosen.

**Results:** We were able to include all 1,029 patients who underwent RARP in the aforementioned period of time. Of these, 18.1% were diagnosed with a lymphocele either when discharged or when readmitted and 6.9% experienced an SLC requiring treatment. Thirteen-point-seven percent of patients readmitted with SLC showed an accompanying thrombosis. Due to recurring or bilateral SLCs receiving different treatment options for each side, there was a total of 115 SLCs treated. CD was carried out in 102 cases. Twenty-point-six percent of patients were sufficiently treated this way, the rest required further treatment or experienced recurrences not requiring further treatment. DI was carried out in 56 cases. Of those patients, 46.4% were sufficiently treated. LF was carried out in 54 cases (either after CD, or after DI, or primarily). Of those patients, 98.1% were treated sufficiently. LF had a statistically significant higher success rate compared to CD and DI (P<0.001 respectively).

**Conclusions:** The study confirmed the significance of SLC as a common complication after RARP. LF turned out to be the most effective treatment option for SLC, while CD as well as DI have not been proven effective.

**Keywords:** Prostate cancer; lymphocele; robot-assisted radical prostatectomy (RARP); laparoscopic fenestration; complication

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## Introduction

Worldwide, prostate cancer is the second most frequently diagnosed cancer (after lung cancer) among men (1), with 1,276,106 new cases (7.1% of all cancer diagnoses in men) and 358,989 deaths (3.8% of all deaths caused by cancer in men) in 2018 (2). At the time of diagnosis, the majority of patients present with an organ-confined stage of the disease. In this case, surgical therapy by means of radical prostatectomy is an established therapeutic option, depending on the life expectancy and comorbidity of the patient (3). Over the course of the last few years many clinics have adopted the robot-assisted laparoscopic radical prostatectomy (RARP) as their new standard of care in surgical therapy of prostate cancer, as it is associated with lower blood loss, lower transfusion rate and less hospitalisation duration in contrast to open radical prostatectomy (4), while also showing good perioperative and oncologic outcomes (4,5).

Intraoperative pelvic lymph node dissection (PLND) is an important component of the surgical therapy of prostate cancer. Although a direct benefit on oncological outcomes has yet to be proven, PLND provides an accurate assessment of cancer spread (6), which is why the current guidelines of the European Association of Urology (EAU) on prostate cancer recommend performing PLND in high-risk patients as well as intermediate-risk patients when the estimated risk for positive lymph nodes (LNs) exceeds 5% (3).

There are, however, complications that are associated with PLND, the most common of which are lymphoceles (6). While most lymphoceles remain clinically asymptomatic, serious complications like infection or venous thromboembolism can occur (7,8). The risk of lymphocele was shown to be higher after extended PLND in comparison to limited PLND (9), no significant difference could be found between the extraperitoneal and the transperitoneal RARP approach (10). In previous studies the percentage of patients presenting with a symptomatic lymphocele (SLC) after prostatectomy and PLND was shown to be between 1.49% and 11.2% (8,10-13). Therapeutic options for the treatment of lymphoceles include cannulation and drainage (CD), instillation (e.g., of doxycycline), or laparoscopic fenestration (LF) (14-17).

The objective of this retrospective study was to explore the frequency of SLC after RARP as well as the effectiveness of different therapeutic options. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/ tau-20-1315).

### **Methods**

We retrospectively analysed all patients who underwent RARP (transperitoneal or extraperitoneal) at our clinic from January 1, 2014 to December 31, 2018. No exclusion criteria were applied. This resulted in a cohort of 1,029 patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee (University of Regensburg, No. 19-1393-104) and individual consent for this retrospective analysis was waived.

We recorded patients' age, height, weight and body mass index (BMI) at the time of RARP, accompanying illnesses and regular anticoagulant or platelet inhibiting medication.

We also recorded patients' prostate-specific antigen (PSA) levels at the time of diagnosis, their risk category according to the d'Amico risk classification for prostate cancer, whether or not preoperative diagnostic imaging had been carried out, and if so, which [abdominal computed tomography (CT), bone scintigram, Ga-68-PSMA-positron emission tomography (PET)/CT] as well as their operational risk according to the American Society of Anesthesiologists (ASA classification).

Regarding the surgery itself we documented, whether or not PLND was conducted, whether or not nerve sparing (NS) was carried out and if so, on which side(s), as well as the final histological result including the TNM stage according to the Union for International Cancer Control (UICC) as well as the Gleason score.

If PLND was conducted, bilateral PLND was performed which included at least the removal of the LNs overlying the external iliac artery and vein as well as the LNs within the obturator fossa cranially and caudally to the obturator nerve. A more extensive PLND was performed in case of pre- or intraoperatively suspect LNs. The lymphatic vessels were sealed by bipolar cauterization, clips were placed in addition according to the surgeon's preference.

From the following days of postoperative hospitalization we recorded the length of the patients' stay, whether or not the first postoperative cystogram (routinely done around the 5th to the 7th postoperative day, according to the surgeon who had performed the procedure) showed an insufficiency of the vesicourethral anastomosis and whether or not a secondary insufficiency of the vesicourethral anastomosis occurred.

The pelvic drainage, which was intraoperatively placed in all cases, was postoperatively removed depending on the drainage output.

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All patients routinely received an ultrasound (US) examination on the day they were discharged, and it was recorded whether or not this examination already showed any lymphoceles and if so, on which side(s).

With regard to deep venous thrombosis (DVT) prophylaxis, all patients received a daily dose of 5,000 IU of low molecular weight heparin (LWMH) for 4 weeks postoperatively. Patients with atrial fibrillation or a history of DVT or pulmonary embolism received a therapeutic or half-therapeutic weight-adapted LWMH dose according to their CHADS-VASc score.

If patients presented with a SLC in our emergency department and were readmitted to our clinic, further data was recorded (referring to the time of presentation at our clinic): the location of the SLC, the patients' body temperature, the following blood test results: leucocyte count, creatinine, estimated glomerular filtration rate (eGFR), whether or not patients reported stress incontinence, as well as local pain upon pressure. All lymphoceles were primarily investigated by US; in some cases an additional CT scan was performed.

Furthermore, we recorded the length of the patients' stay after readmission as well as the following parameters: concomitant venous thrombosis, the SLC treatment(s) applied [CD, instillation of doxycycline (including frequency and duration of instillation) or LF], if an antibiotic treatment was initiated and if the discharge examination by US showed persistent lymphoceles. Primary treatment for SLC was chosen at the surgeons' discretion. Any therapeutic approach used to treat a case of SLC was defined as successful if the patient did not experience a recurrence and did not require further treatment.

If CD of the lymphocele was conducted, we recorded the result of the bacteriological diagnostics of the lymphocele fluid. Patients were not recorded as SLC cases when a creatinine measurement after drainage placement revealed the fluid collection to be a urinoma.

For every patient, we recorded the result of the urine culture when readmitted.

## Statistical analysis

Statistical analysis was performed using SPSS (version 25). The statistical tests used to describe the relation between binary variables were chi-squared test as well as Fisher's exact test. To describe the relation between binary and quantitative variables, Mann-Whitney U test was used after taking into account the skewness.

## **Results**

#### Patient population

We were able to include all 1,029 patients who underwent RARP in the aforementioned period of time. Median age of all patients was 65.5 years [interquartile range (IQR), 60.0–70.0 years], median PSA level was 8.31 ng/mL (IQR, 6.00–12.83 ng/mL), with 275 patients having low-risk, 420 patients having intermediate-risk and 332 patients having high-risk disease, respectively. A detailed overview of the study population is shown in *Table 1*.

# High BMI and high postoperative Gleason score correlate with the occurrence of SLC

There were no statistically significant correlations between the occurrence of SLC and patients' age, their histological tumour stage including LN status, the number of LNs removed during PLND, their initial PSA levels and their risk classification according to d'Amico.

It could be shown, however, that patients with SLC had a significantly higher median BMI compared to those without SLC (29.6 vs. 27.2, P<0.001). Also, SLC was shown to be more likely among patients with a high postoperative Gleason score (P=0.017). Both higher BMI (P<0.001) and high postoperative Gleason score (P=0.016) remained statistically significant in multivariable analysis.

### Frequency of SLC

Of the 1,029 patients who underwent RARP in the aforementioned period of time, a total of 186 patients (18.1%) were diagnosed with a lymphocele, either during the standard discharge examination or when readmitted to our clinic. Seventy-three patients after RARP (7.1%) were readmitted because of a SLC, 71 of whom (6.9% of all patients who underwent RARP) had to undergo treatment. The main symptoms of these patients were local pain upon pressure and signs of infection.

In total, 115 cases of SLC were treated in the described period of time and thus included in this study. This is due to several patients being treated because of their SLC, discharged, and later readmitted because of a recurrence. Furthermore, some patients showed bilateral SLC, which were treated with varying degrees of success or different therapeutic options. A detailed overview of the patients with SLC is shown in *Table 2*. Table 1 Patient characteristics

Characteristics	Patients without SLC	Patients with SLC	All patients	Р
Age in years, median [min.; max.]	65.0 [39.0; 81.0]	65.0 [50.0; 78.0]	65.0 [39.0; 81.0]	0.726
BMI in kg/m², median (min.; max.)	27.2 (18.1; 45.8)	29.6 (21.6; 40.5)	27.9 (18.1; 45.8)	<0.001
Histological TNM-stage, number (%)				
Not recorded	1 (0.1)	0 (0.0)	1 (0.1)	-
pT1a*	1 (0.1)	0 (0.0)	1 (0.1)	0.233
pT1b*	1 (0.1)	0 (0.0)	1 (0.1)	
pT1c	0 (0.0)	0 (0.0)	0 (0.0)	
pT2a	64 (6.7)	5 (7.0)	69 (6.7)	
pT2b	40 (4.2)	7 (9.9)	47 (4.6)	
pT2c	531 (55.4)	39 (54.9)	570 (55.4)	
рТЗа	191 (19.9)	8 (11.3)	199 (19.3)	
pT3b	124 (12.9)	12 (16.9)	136 (13.2)	
pT4	5 (0.5)	0 (0.0)	5 (0.5)	
pN0	790 (82.5)	65 (91.5)	855 (83.1)	0.849
pN1	67 (7.0)	6 (8.5)	73 (7.1)	
No PLND	101 (10.5)	0 (0.0)	101 (9.8)	
M0	958 (100.0)	70 (98.6)	1,028 (99.9)	-
M1	0 (0.0)	1 (1.4)	1 (0.1)	
LN removed, median [IQR]	16 [12; 22]	17 [4; 21]	16 [12; 22]	0.971
PSA level in ng/mL, median (min.; max.)	8.30 (0.28; 207.60)	8.61 (0.90; 371.00)	8.31 (0.28; 371.00)	0.718
Postoperative Gleason score, number (%)				0.017
Not recorded	4 (0.4)	0 (0.0)	4 (0.4)	
6	136 (14.2)	5 (7.0)	141 (13.7)	
7a	489 (51.0)	35 (49.3)	524 (50.9)	
7b	220 (23.0)	16 (22.5)	236 (22.9)	
8	31 (3.2)	3 (4.2)	34 (3.3)	
9	75 (7.8)	12 (16.9)	87 (8.5)	
10	3 (0.3)	0 (0.0)	3 (0.3)	
D'Amico risk classification, number (%)				0.259
Not recorded	2 (0.2)	0 (0.0)	2 (0.2)	
Low risk	259 (27.0)	16 (22.5)	275 (26.7)	
Intermediate risk	393 (41.0)	27 (38.0)	420 (40.8)	
High risk	304 (31.7)	28 (39.4)	332 (32.3)	

\*, patient had pT1a or pT1b tumor in transurethral resection and no tumor in prostatectomy. SLC, symptomatic lymphoceles; IQR, interquartile range.

### Treatment of SLC: fenestration as the only effective option

The therapeutic options used were CD, instillation of doxycycline and LF. A detailed description of how these therapeutic measures were applied to the 115 cases of SLC is shown in *Figure 1*. Any therapeutic approach used to treat a case of SLC was defined as successful if the patient did not experience a recurrence and did not require further treatment. This refers to the specific case of SLC treated; a contralateral recurrence, for example, was defined as a

Table 2 Patients with symptomatic lymphoceles

Characteristic	Number			
Readmissions due to SLC after RARP	73			
Treatment of SLC	71			
Number of readmissions due to SLC recurrence after SLC treatment				
0	59			
1	9			
2	1			
3	2			
All readmissions receiving treatment of SLC	88 (59+9×2+1×3+2×4)			
Location of treated SLC				
Unilateral left	29			
Unilateral right	32			
Bilateral	25			
Prevesical	2 (both bilaterally treated)			
Total cases of treated SLC	115 (29+32+25+25+2+2)			
SIC symptomatic lymphoceles: BARP robot-assisted radical				

SLC, symptomatic lymphoceles; RARP, robot-assisted radical prostatectomy.

separate case.

The success rates of the different approaches are shown in Figure 2. In total, 102 cases of SLC received CD. Of those, 21 cases (20.6%) were successfully treated this way. The rest required further treatment or experienced a recurrence of the SLC. In 56 cases of SLC, the next treatment option chosen was instillation of doxycycline, which proved successful in 26 cases (46.4%). LF of the SLC was applied in 54 cases (in 21 cases following CD as well as instillation of doxycycline, in 20 cases following CD only, and in 13 cases as primary therapeutic option). Fiftythree cases of SLC (98.1%) were successfully treated this way, corresponding to 20 cases of LF after CD as well as instillation of doxycycline (95.2%), 20 cases of LF after CD only (100.0%) and 13 cases of primary LF (100.0%). The success rate of LF was significantly higher than the success rates of CD and drainage and instillation (DI) (P<0.001, respectively).

### **Complications of SLC**

As mentioned before, SLC can present with several complications such as thromboembolism or infection. Of those readmitted because of SLC, 10 patients (13.7%) presented with an accompanying deep vein thrombosis. With regard to infection of the SLC, in 23 of the 88 (26.1%) readmissions due to SLC the bacteriological diagnostic of the SLC fluid after cannulation showed bacteria. The bacteria which could be found and their frequency distribution are shown in *Table 3* (in one case, the SLC culture showed a colonisation with two bacteria). Most of these bacteria are commensal with low pathogenic potential. This results in 8 of 88 (9.1%) readmissions with pathogenic bacteria in SLC culture (*Table 3*).

Of the 88 hospital readmissions due to SLC, 10 patients

	Cases of SLC per therapy sequence and success rate					Successfully treated (%)
	Cannulation and drainage	Cannulation and drainage	Cannulation and drainage	Cannulation and drainage		21/102 (20.6%)
		Instillation of doxycycline	Instillation of doxycycline			26/56 (46.4%)
			Laparoscopic fenestration	Laparoscopic fenestration	Laparoscopic fenestration	53/54 (98.1%)
SLC cases	26	35	21	20	13	115

Figure 1 Cases of SLC per therapy sequence and therapeutic option. SLC, symptomatic lymphoceles.

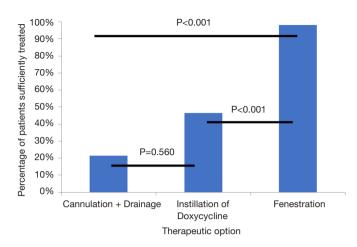


Figure 2 Success rates of different therapeutic approaches. Chi-squared test, P<0.05 indicates statistically significant results.

Table 3 Bacteria from SLC cultures and their frequency

Bacteria	Number	Pathogenic
Streptococcus agalactiae	4	
Staphylococcus epidermidis	4	
Escherichia coli*	2	Х
Staphylococcus aureus*	2	Х
Peptostreptococcus anaerobius	2	
Staphylococcus lugdunensis	2	
Streptococcus constellatus	1	
Staphylococcus hominis	1	
Enterococcus faecium*	1	Х
Enterococcus faecalis*	1	Х
Corynebacteria	1	
Streptococcus gallolyticus	1	
Citrobacter koseri*	1	Х
Bacteroides fragilis*	1	Х

\*, pathogenic bacteria. SLC, symptomatic lymphoceles.

(11.4%) presented with fever (defined as a body temperature above 38.4 °C), while another 6 patients (6.8%) presented with an elevated body temperature between 37.5 and 38.4 °C. An accompanying urinary tract infection as shown by a positive urine culture could be found in 31 patients (35.2%). The overlap of patients presenting with elevated body temperature above 37.5 °C, a positive SLC culture and a sterile urine culture showed a total of 6 patients equalling

6 cases of SLC (6.8% of all readmissions due to SLC, 5.2% of all treated cases of SLC).

## **Discussion**

RARP has emerged as the new standard of care for surgical treatment of prostate cancer. However, SLC remain a common complication even with this minimally invasive method, regardless of the approach (extraperitoneal or transperitoneal) (10).

As mentioned above, in previous studies the percentage of patients presenting with SLC after prostatectomy and PLND was shown to be between 1.49% and 11.2% (8,10-13). With 7.2% of all RARP patients experiencing SLC, our study showed a frequency of SLC similar to those reported previously. The variance of the reported frequencies may in part be due to the use of different imaging techniques (US *vs.* CT scan) to detect SLC.

PLND had previously been shown to be the main risk factor for SLC formation after RARP (18). Correspondingly, our data showed that patients who did not receive PLND were significantly less likely to develop SLC (P<0.001). As additional risk factors for SLC formation previous studies listed patients' age, BMI and the number of LNs removed (8,13,19). Our study, however, showed patients' BMI and their postoperative Gleason score to be the only statistically significant risk factors for SLC, with patients with high BMI (P<0.001) and patients with a high postoperative Gleason score (P=0.017) being more likely to experience SLC.

Regarding therapy of SLC, there is no standard of

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care, with different therapeutic approaches having been reported with varying rates of success. While some authors recommend that LF be used as first-line treatment for SLC (14,15), others report success rates of 70% to 100% for conservative approaches (8,17,20). The success rates for LF given by the aforementioned studies are 97% to 100%, with a mean hospitalisation time of 2.3 days postoperatively (14,15). Our success rate of 98.1% for LF in general (100% for primary LF) is well comparable to these results. Comparison of success rates for instillation therapy, however, is made difficult by the fact that in the aforementioned studies povidone-iodine and ethanol were used as sclerosing agents, whereas we used doxycycline. Apart from that, no differences can be found in conducting the instillation therapy. In our study, LF of the SLC proved significantly more effective than CD (P<0.001) and instillation of doxycycline (P<0.001). There was no significant difference between the two conservative approaches (P=0.560).

Furthermore, our patients' average time of hospitalisation (from admission until discharge) depended on their therapy sequence and was found to be 7 days for CD only, 12 days for CD followed by instillation of doxycycline, 14 days for CD followed by instillation of doxycycline followed by LF, and 9 days for primary LF. The mean hospitalisation time of 9 days for our primary LF patients is longer in comparison to the one given by the aforementioned studies. This is explained by the delay until reaching the decision to conduct primary LF and getting a slot in the operating room. By reducing the time from admission to primary LF (for example, by establishing primary LF as the standardised treatment option for SLC), the total time of hospitalisation for SLC patients can probably be reduced even further (3–4 days).

Thromboembolism is described as a common complication of SLC, with reported rates of deep vein thrombosis of up to 8% for patients with lymphoceles (20). PLND is a known risk factor for thromboembolic events (21). In our study, 13.5% of patients presenting with SLC also experienced a deep vein thrombosis. As most other studies only show the percentage of deep vein thrombosis in relation to all patients receiving RARP and not in relation to patients experiencing SLC, a precise evaluation of this percentage is difficult.

Infection is also often mentioned as a complication of SLC. Infection of SLC as indicated by a positive SLC culture and a sterile urine culture was reported by Hamada *et al.* to affect up to 42% of SLC after RARP, with *Staphylococcus aureus* being the most frequently isolated organism (11). In our study, in 26.1% of readmissions due to SLC the bacteriological diagnostic of the SLC fluid after cannulation showed bacteria. Most of these bacteria, however, are commensal with low pathogenic potential or possibly due to contamination (*Table 3*), which results in 9.1% of readmissions presenting with pathogenic bacteria in SLC culture.

Hamada *et al.* furthermore reported that fever, CT findings of abnormally thickened walls, leucocytosis and younger age were significant predictors for SLC fluid culture positivity (11).

In our study, however, no significant correlation between a positive SLC culture and elevated body temperature, leucocytosis, elevated C-reactive protein (CRP) or lower abdominal pain could be found. There often was an accompanying urinary tract infection, which is another possible reason for fever and elevated inflammation markers.

As previously described, the overlap of patients presenting with elevated body temperature above 37.5 °C, a positive SLC culture and a sterile urine culture showed a total of 6 cases of SLC (6.7% of all readmissions due to SLC, 5.2% of all treated cases of SLC). Thus, a clinically significant infection of a SLC is a rare complication.

## Conclusions

SLC are a common postoperative complication of RARP. However, serious complications like deep vein thrombosis or clinically relevant infections of SLCs with pathogenic bacteria are rare. Our retrospective analysis shows that the most efficient treatment method for SLC is LF, which also results in a shortened hospital stay and should be considered as the initial treatment of SLC. However, an additional cost-benefit-analysis as well as larger prospective studies are necessary to further confirm this recommendation.

## Limitations

The main limitation of this study is its retrospective design over a time period of five years. On the one hand, this makes analysis of the parameters of interest more difficult, as surgical techniques and clinical approaches are in constant change. On the other hand, we were able to acquire a comparatively large number of patients, which certainly contributes to the relevance of the reported results. Certainly, though, further prospective data is necessary to confirm the reported results.

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